ABSTRACT OF THE DISCLOSURE

The present invention provides a genetic method for tethering polypeptides to the yeast cell wall in a form accessible for binding to macromolecules. Combining this method with fluorescence-activated cell sorting provides a means of selecting proteins with increased or decreased affinity for another molecule, altered specificity, or conditional binding. Also provided is a method for genetic fusion of the N terminus of a polypeptide of interest to the C-terminus of the yeast Aga2p cell wall protein. The outer wall of each yeast cell can display approximately 104 protein agglutinins. The native agglutinins serve as specific adhesion contacts to fuse yeast cells of opposite mating type during mating. In effect, yeast has evolved a platform for protein-protein binding without steric hindrance from cell wall components. As one embodiment, attaching an scFv antibody fragment to the Aga2p agglutinin effectively mimics the cell surface display of antibodies by B cells in the immune system for affinity maturation in vivo. As another embodiment, T cell receptor mutants can be isolated by this method that are efficiently displayed on the yeast cell surface, providing a means of altering T cell receptor binding affinity and specificity by library screening.